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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,696	01/19/2001	Daniel S. Sem	P-TB 4567	6467

23601 7590 11/23/2001

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EXAMINER	
GARCIA, MAURIE E	

ART UNIT	PAPER NUMBER
1627	10

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/765,696	Sem
Examiner	**Art Unit**
Mauri E. Garcia, Ph. D.	1627

-- Th MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 30, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-14* is/are pending in the applica

4a) Of the above, claim(s) *1-8* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *9-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. The Response filed August 30, 2001 (Paper No. 8) is acknowledged. No claims were amended, added or cancelled. Therefore, claims 1-14 are pending.

Election/Restriction

2. Applicant's election, with traverse, of Group II (claims 9-14) and election of species is acknowledged. The traversal is addressed below.

3. Applicants traverse the Restriction Requirement with respect to the separation of the claims of Group I from Group II and state that combined search and examination would not create an undue burden (see Response, page 2). Applicant also argues that the classification of the two groups is similar. However, the examiner maintains that the inventions are distinct for the following reasons.

4. As stated in the Restriction Requirement, Groups I and II are different methods. The methods are different because they use different steps and will produce different products. They therefore have different issues regarding patentability and enablement and represent patentably distinct subject matter. In the instant case, the method of generating the library (Group I) generates a "population of bi-ligands comprising a plurality of identical modules attached to variable second ligands". The process of identifying a population of bi-ligands (Group II)

generates a "population of bi-ligands, wherein said bi-ligand comprises said modules and a second ligand linked by said expansion linker"; note there is no requirement for the identical modules and variable second ligands in this group.

5. Again, as stated in the Restriction Requirement, there is no expectation that the searches of these two groups would be coextensive. This is especially true for searches of the non-patent literature, which are not affected by the classification of the instant claims. Therefore, this does create an undue search burden. The requirement is still deemed proper and is therefore made FINAL.

6. Claims 1-8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 8.

7. With respect to the species election, applicant requests that certain species be examined together (Response, page 4). Applicant also notes that an election of species is a "provisional election". Concerning examining species together, applicant did not submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case (see Restriction Requirement, paragraph 13).

8. Concerning the fact that an election is a "provisional election", the following is noted. See MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species***. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

9. Applicant's specifically elected species was searched and was not found in the prior art. Thus, the search was expanded to non-elected species which *were* found in the prior art, see rejections below.

10. Therefore, claims 9-14 are examined on the merits in this action.

Information Disclosure Statement

11. Upon review of the instant case, the examiner has found only one Information Disclosure Statement (IDS), namely Paper No. 4, filed May 7, 2001. This IDS has been considered and a signed copy of the PTO-1449 is attached to this action. However, it appears from the file history that there may have been another IDS filed on May 3, 2001. If this is the case, the IDS filed May 3, 2001 is missing from the instant case. Clarification/correction is respectfully requested.

Drawings

12. The drawings filed with the application are acceptable for examination and are approved by the PTO draftsman.

Specification

13. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser- executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser- executable code. See MPEP § 608.01. The lengthy specification has not been checked to the extent necessary to determine the presence of all instances of the above codes; however, see for example, page 19, line 31 and page 20, line 29.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Applicant's claims are directed to a "method for identifying a population of bi-ligands". The claims use generic terminology such as "common ligand", "conserved site", "second ligand", "specificity site", "receptor family" and "expansion linker". These terms are defined in the instant disclosure but the definitions are very broad.

The specification discloses **no** examples of the preparation and use of such "population of bi-ligands". These compounds are made up of pieces (i.e. "common ligand" and "second ligand") that could encompass very different moieties such as peptides and organic molecules. Additionally, the descriptions of "conserved site" as residues that are sufficient for activity (specification, pages 13-14) and "specificity site" as a binding site for a ligand exhibiting specificity for a receptor (specification, page 15) are simply not adequate support to show possession of the claimed invention. The disclosure is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members which are yet to be prepared or envisioned. This further evidences that instant disclosure does not constitute support for the claimed genus or a substantial portion thereof.

16. Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The breadth of the claims and the nature of the invention: The claims are drawn to a "method for identifying a population of bi-ligands". No limitations on the specific structure of the "bi-ligand" are given and, as such, this could read on a wide variety of structures. The invention is such that each of the components must be present in operable form for successful practice of the invention. For example, the "common ligand" and "second ligand" must bind to their respective sites and the sites must be able to be determined.

The state of the prior art and the level of predictability in the art: Compounds having two binding sites that bind to receptors such as kinases were known at the time of filing (see art rejections below); however, only limited numbers of such compounds were known and the specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of *any* such compound. The "bi-ligands" of the instant claims require "common ligands" and a "second ligand"; however, such ligands were not generally known in the art. The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict their structures (and thus how to make such compounds) in the absence of any guidance without undue experimentation. Applicant's claimed scope of compounds represents only an invitation to experiment regarding possible ligands and linkers of undefined structure.

Moreover, the claims require the presence of a "common ligand" to a "conserved site" and a "second ligand" to a "specificity site". One of ordinary skill would not know, a priori, how to determine such ligands and, most importantly, how to determine the conserved and specificity sites since this is a very unpredictable area of the art. This is especially true since the conserved site must be conserved across a receptor family. The instant specification fails to identify that structure which is required for the claimed activity.

The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. Such persons of ordinary skill in this art, given its unpredictability, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

The existence of working examples and the quantity of experimentation needed to make or use the invention based on the content of the disclosure: Applicants have provided **no** working examples and the state of the prior art is such that one of ordinary skill could not predict how to determine a "conserved site" for a receptor family, find a "common ligand" thereto, and further find a "second ligand" to a "specificity site" as required by the instant claims. The instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the claimed invention. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the invention would require undue experimentation.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "receptor" is indefinite because it lacks clear antecedent basis in claim 9. There are both "receptors" in claim 9 (page 54, line 20) and "a receptor in said receptor family" (page 54, lines 26-27) and it is unclear to which receptor claim 11 is referring.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

20. Claims 9-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Combs et al (On PTO-1449; JACS, 1996, Vol. 118, No. 1, pp. 287-288).

The following interpretations are used for this rejection:

The specification defines a population as "a group of two or more different molecules" (page 14, line 4). Combs et al disclose making two or more different molecules that comprise a common ligand (the biasing sequence PLPPLP) and a specificity ligand linked by a linker. As illustrated by the binding assays, these ligands

can bind at least 2 SH3 domains from different receptors in the same family (Src and PI3K). These domains are found in kinases (reading on instant claim 11) which bind ATP as a cofactor (reading on instant claim 12). The linker in these compounds (Figure 3 of the reference) could be either of two possibilities as explained in detail below. The definition in the specification of "expansion linker" (page 9-10) is very broad and both of the options described below would clearly be encompassed by applicant's definition. The linker of the reference has a specific stereochemistry and would comprise a linker possessing perfect C2 symmetry as defined in the specification on page 10 (instant claims 13-14).

Specifically, Combs et al disclose making "a library of ligands that direct non-peptide binding elements in to the specificity pocket of SH3 proteins" (see Figure 1). These ligands have two binding sites; "a common low affinity biasing sequence PLPPLP" and 32 "capping reagents" that have the potential to bind in the specificity pocket (see page 287). Therefore, PLPPLP sequence would comprise the common ligand and the capping reagents the specificity ligands. These compounds were assayed against the SH3 domain from the protein kinase Src and at least 7 ligands were identified that bind (see Figure 3 and Table 1). The linker in these 7 compounds could be considered to be either of the following: (a) the carboxylic group linking the PLPPLP to the non-peptide portion; (b) the structure denoted **1** in Figures 2 and 3. Thus, the linker (interpreted as above) and the PLPPLP sequence read on the claimed "module", with the different capping reagents of Combs reading on the "second ligand" of the instant claims.

Ligand 1A was also measured against the SH3 domain in the p85 component of PI3K and did show binding for this domain, although it showed selectivity for Src SH3. This reads on the limitations of the instant claim 10.

21. Claims 9-14 are rejected under 35 U.S.C. 102(b) as being anticipated by He et al (On PTO-1449; Bioorg. Med. Chem. Lett., 1994, Vol. 4, No. 4, pp. 2845-2850).

The following interpretations are used for this rejection:

The specification defines a population as "a group of two or more different molecules" (page 14, line 4). He et al disclose making two or more different molecules that comprise a common ligand (an ATP mimic) and a specificity ligand linked by a linker. As taught by the reference, these ligands can bind at least 2 different receptors from the same family (kinases) which bind ATP as a cofactor (reading on instant claims 10-12). The linker in the compounds of He et al is a simple methylene chain of variable length and as such would comprise a linker possessing perfect C2 symmetry as defined in the specification on page 10 (claims 13-14).

Specifically, He et al discuss the fact that kinases have two binding sites in the catalytic domain; one of these sites binds ATP while the other binds peptidic substrates (page 2845). He et al disclose making bisubstrate inhibitors "suitable to interact simultaneously with the ATP and the protein substrate binding domains" (page 2845, 2nd paragraph). The compounds contain an ATP mimic that would comprise the common ligand stated in the instant claims since this is a known "natural common ligand" for

kinases (see specification, page 8-9). These compounds are of the general structure shown in Figure 2, with specific examples in Table 1. This ligand (ATP mimic) plus the methylene chain linker read on the claimed "module", with the different second ligands of He reading on the "second ligand" of the instant claims. He discloses second ligands that are either an amine or an amino acid. The second ligand creates differences in the binding of the compounds with two different kinases, protein kinase C and c-AMP dependent protein kinase, as shown in Table 1. Changes in this second ligand are made due to differences in the binding sites of the two different kinases (page 2849), reading on the limitations of claim 10.

Status of Claims/ Conclusion

22. No claims are allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie E. Garcia, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 8:30 to 6:00.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of

a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie E. Garcia, Ph.D.
November 19, 2001

MAURIE E. GARCIA, Ph.D
PATENT EXAMINER